RESEARCH ARTICLE

A mathematical model of synaptotagmin 7 revealing functional importance of short-term synaptic plasticity

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Funding: *This study was supported by a grant from Lincoln University, New Zealand.*

Abstract

Synaptotagmin 7 (Syt7), a presynaptic calcium sensor, has a significant role in the facilitation in short-term synaptic plasticity: Syt7 knock out mice show a significant reduction in the facilitation. The functional importance of short-term synaptic plasticity such as facilitation is not well understood. In this study, we attempt to investigate the potential functional relationship between the short-term synaptic plasticity and postsynaptic response by developing a mathematical model that captures the responses of both wild-type and Syt7 knock-out mice. We then studied the model behaviours of wild-type and Syt7 knock-out mice in response to multiple input action potentials. These behaviors could establish functional importance of short-term plasticity in regulating the postsynaptic response and related synaptic properties. In agreement with previous modeling studies, we show that release sites are governed by non-uniform release probabilities of neurotransmitters. The structure of non-uniform release of neurotransmitters makes short-term synaptic plasticity to act as a high-pass filter. We also propose that Syt7 may be a modulator for the long-term changes of postsynaptic response that helps to train the target frequency of the filter. We have developed a mathematical model of short-term plasticity which explains the experimental data.

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doi: *10.4103/1673-5374.247466*

Received: *August 21, 2018*
Accepted: *November 2, 2018*

Key Words: *synapse; short-term plasticity; short-term facilitation and depression; mathematical model; low-frequency stimulation; high-frequency stimulation*

Chinese Library Classification No. *R459.9; R311*

Introduction

Synapses have been shown to undergo dynamical modulations in postsynaptic responses following stimulation by specific patterns of action potentials at the presynaptic terminal. Short-term plasticity is one of the main forms of plasticities displayed in central neurons (Citri and Malenka, 2007). Short-term synaptic plasticity denotes the modulation that lasts from tens of milliseconds to a few minutes. It originates from presynaptic mechanisms through modulating the presynaptic release probability and the site availability for release (Regehr, 2012). The plastic nature of synaptic transmission provides a theoretical basis for information transfer and memory formation (Martin et al., 2000; Klyachko and Stevens, 2006).

Short-term facilitation and depression are typical forms of short-term synaptic plasticity in central synapses (Zucker and Regehr, 2002). In synapses displaying short-term facilitation, postsynaptic response by the second of two closely spaced presynaptic action potential (APs) is larger than that by the first one, and thus synapses show increased synaptic efficacy (Regehr, 2012). On the contrary, short-term depression refers to a lower postsynaptic response by the second of two closely spaced presynaptic APs compared to the postsynaptic response by the first one, and leads to a reduction in synaptic strength. Mostly, synaptic strength results from a combination of short-term facilitation and depression, depending on the timing of presynaptic stimulation (Zucker and Regehr, 2002). However, the functional importance of short-term plasticity in the synapse is not well understood.

Facilitation can enhance the information coding and transmission across a synapse by promoting the neurotransmitter release by presynaptic stimulation (Abbott and Regehr, 2004). The mechanism underlying the facilitation in Schaffer collaterals (SCs) remains a mystery and is different from the Ca^{2+} buffer saturation mechanism, which accounts for the facilitation in several critical brain areas (Blatow et al., 2003; Jackman et al., 2016). Jackman et al. (2016) reported that synaptotagmin 7 (Syt7), a calcium sensor located in the presynaptic terminal, has a significant role in the facilitation in SCs. Syt7 has a number of functions including asynchronous release (Bacaj et al., 2013), replenishing the release site (Liu et al., 2014), and secretion of large molecules (Martinez et al., 2000; Gustavsson et al., 2008). When Syt7 is knocked out in several central areas, including SCs, a significant reduction in presynaptic facilitation has been observed. Hence, the functional importance of short-term plasticity in the synapse would be further revealed by investigating the roles of Syt7.

Given the complexity and variability of synaptic transmission and plasticity (Dobrunz and Stevens, 1997; Murthy et al., 1997; Bliss et al., 2013), it is difficult to understand the potential roles of Syt7, as well as Syt7 dependent short-term synaptic plasticity, because of poor understanding of the mechanisms linking short-term plasticity to synaptic functions. But there are serious attempts to understand these mechanisms over the last few decades. There are three pools

of synaptic vesicles in the presynaptic terminal (Neves and Lagnado, 1999) which are usually categorized as (1) a readily releasable pool (RRP) which rapidly releases, (2) a recycling pool which releases more slowly, and (3) a reserve pool which releases most slowly [reviewed in Denker and Rizzoli (2010) and Rizzoli and Betz (2005)]. Quantal release hypothesis, where a 'quanta' of neurotransmitters, corresponding to the number of neurotransmitters contained in a single vesicle, evokes miniature excitatory postsynaptic current (mEPSC) (del Castillo and Katz, 1954). We now understand the factors that regulate the probability of vesicle release: the release requires 10–100 μM local Ca^{2+} concentration around Ca^{2+} sensors which conduct the release; and the release can be enhanced by build-up of the residual Ca^{2+} concentration (Ca_{res}), which is the remaining free Ca^{2+} after buffering and transporting out of the terminal (Felmy et al., 2003; Regehr, 2012).

We still do not understand the mechanism underlying the transitions of vesicles among the three pools of synaptic vesicles. A number of hypotheses are proposed as to the nature of vesicle release at central synapses, and there are contentious issues related to the single vesicular release (Biró et al., 2005; Dobrunz and Stevens 1997; Stevens and Wang 1995), and the multivesicular release (Schneggenburge et al., 2002; Conti and Lisman 2003; Christie and Jahr 2006). Furthermore, a vesicle can be released in either of the two modes in the hippocampus: (1) kiss and run, where a small portion of the neurotransmitters contained in a vesicle is released, and (2) full fusion, where all the contained neurotransmitters are released [reviewed in Regehr (2012) and Klyachko and Stevens (2006)]. However, how a vesicle switches between the two modes is unclear.

Mathematical modeling is one of the ways to obtain insights into unknown mechanisms based on plausible reasoning. In this study, a general model was developed based on current understanding of the mechanistic relationships of synapse. In this general model, there are a subset of parameters that are common to both wild-type and Syt7 knockout neurons in SCs of mice (Jackman et al., 2016). The values of the set of parameters excluding the common parameter sets depend on wild-type and knockout experimental data. These two separate sets of parameter values are estimated to capture the behavioural difference in neurons in SCs between wild-type and Syt7 knockout mice based on the limited experimental data. The general model and the two sets of parameters enable us to capture the behavioral differences, if any, between wide-type and Syt7 knockout mice through the computational experiments. Since Syt7 drives short-term facilitation, a behavioral difference in Syt7 KO mice indicates potential functional importance of Syt7 and Syt7 driven short-term plasticity.

Models of short-term plasticity in previous studies (Dittman et al., 2000; Sun et al., 2005) can only partially capture the trends in experimental data; they fit either WT or Syt7 KO mice, but not both. Using our model, we understand that (1) release sites are governed by non-uniform release probabilities in SCs as shown in the experiments (Walmsley et al., 1988; Rosenmund et al., 1993; Silver, 2003; Trommershäuser et al., 2003): there are at least two sets of release sites; the majority have low release probability (low sites) and the minority have high release probability (high sites) while previous models are formulated based on one set of release sites. In agreement, another computational study also reported heterogeneity in presynaptic release probabilities in the giant synapses in calyx of Held (Trommershäuser et al., 2003) indicating that the heterogeneity of presynaptic release probabilities across different types of synapses may exist; (2) the basal transmission is contributed by high sites, and short-term facilitation is contributed by low sites; and (3) Syt7 KO mice have significant alterations on high sites during low-frequency stimulation and on low sites during high-frequency stimulation. This result suggests that Syt7 may select release sites depending on the release probability and stimulation frequency.

We proposed that Syt7 selects release sites to undergo short-term synaptic plasticity and modulates the release profile of a synapse in SCs. In addition to short-term synaptic plasticity, SC synapses also undergo long-term plasticity when subjected to low-frequency stimulation and high-frequency stimulation.

Materials and Methods

Determination of presynaptic Ca^{2+} dynamics

The rise of the presynaptic Ca^{2+} level is modeled as the normalization by the amount of Ca^{2+} influx triggered by presynaptic Aps. The use-dependent changes of Ca^{2+} influx are ignored so that the Ca^{2+} influx is fixed across APs (Regehr, 2012; Jackman et al., 2016). Each action potential elevates presynaptic Ca^{2+} level by a fixed amount, ΔCa, and the resulting Ca^{2+} rise decays with a time constant τ_{ca}. However, Ca^{2+} decay may not be governed by a single exponential function: the decay may be biphasic (Collin et al., 2005). Therefore, we use a Hill function to represent the decay rate according to the Ca^{2+} level. The ordinary differentiation equation governing the Ca^{2+} level (Ca) is given by Eq. (1). (Here the rate of change of Ca^{2+} concentration is denoted by dCa/dt and t is time.)

$$\frac{dCa}{dt} = -\frac{Ca}{\tau_{ca}}\left(\frac{1}{1+\left({}^{Kca}/_{Ca}\right)}\right) + \Delta_{Ca}\delta\left(t - t_{ap}\right) \quad (1)$$

where Kca is the dissociation constant for Ca^{2+} decay, $\delta(t–t_{ap})$ is the Kronecker delta function, Δ_{ca} is the normalized rise of Ca^{2+}, which is fixed to 1 in this model, after each action potential stimulation, and t_{ap} is the time that an AP arrives at the presynaptic terminal.

A mathematical model of short-term synaptic plasticity

Short-term depression

Depression is mainly caused by the reduction in the availability of release sites in response to closely spaced presynaptic APs when the inter-action potential interval is insufficient for the recovery from the depletion due to any releases. The reduction has a number of presynaptic causes, including the depletion of release sites and vesicle pools, the inacti-

vation of release sites, and the inactivation of Ca^{2+} channel (Regehr, 2012). The reduction may also be caused by postsynaptic factors such as postsynaptic receptor saturation or desensitization which decrease miniature ESPC (Chen et al., 2002; Sun and Beierlein, 2011). The depression undergoes two major phases: a refractory phase which prevents the response of the release site from further action potential and followed by a recovery phase which exhibits reduced availability of the release site (Stevens and Wang, 1995; Dobrunz et al., 1997; Hjelmstad et al., 1997). We used *X*, *Y*, and Z to reflect average fractions of sites at releasable, releasing and refractory states, respectively, and $X + Y + Z = 1$ (Sun et al., 2005). The changes of *X*, *Y* and *Z* are modeled as three ordinary differentiation equations (Sun et al., 2005), as given by equations (2), (4) and (5) in later paragraphs.

In this setup, both releasing and refractory states are un-releasable and the recovery phase of depression is reflected by the transition of the refractory fraction into the releasable fraction. Hence, the reduction in the availability of release sites as a whole is reflected by the increased fractions of release and refractory sites. In addition, the very slow vesicle refilling process by endocytosis is ignored by assuming the three vesicle pools (Rizzoli and Betz, 2005; Denker and Rizzoli, 2010), with greater than 500 vesicles (Rizzoli and Betz, 2005; Denker and Rizzoli, 2010), are sufficient to replenish the release site without refilling during high frequency stimulation, at least for a small number of stimuli. The differences in replenishing rates among the pools (Rizzoli and Betz, 2005) are ignored because they are less significant for a small number of stimuli.

Once a presynaptic action potential arrives at the presynaptic terminal, only releasable sites can release a vesicle with a mean probability of P_r. After releasing, releasable sites transfer into the releasing state instantaneously. At the same time, refractory sites are recovering from depression to releasable state with a recovery rate of k_{rec}. Thus, the change of the fraction of releasable sites X with time (Dittman et al., 2000; Sun et al., 2005) is

$$\frac{dX}{dt} = -P_r X \cdot \delta\left(t - t_{ap}\right) + k_{rec} \cdot Z \tag{2}$$

The recovery rate k_{rec} has a slow basal component and a faster Ca^{2+} controlled component as given by:

$$k_{rec} = k_0 + \frac{k_{max} - k_0}{1 + \left({}^{Kr}/_{Ca(t)}\right)^{nr}} \tag{3}$$

where k_0 is the basal recovery rate, k_{max} is the faster recovery rate, K_r is the dissociation constant, Ca is the normalized presynaptic Ca^{2+} rise following the AP in equation (1) and n_r is the Hill coefficient. Here, the Hill equation is used to reflect a switch-like behavior of the faster recovery rate having the normalized presynaptic Ca^{2+} level as the control parameter. After release of vesicles, the sites enter a brief releasing state before becoming refractory, such that

$$\frac{dY}{dt} = P_r X \cdot \delta\left(t - t_{ap}\right) - \frac{Y}{\tau_{in}} \tag{4}$$

where τ_{in} is the time constant for the transition into refractory states.

Finally, the change of the fraction of refractory sites *Z* with time is determined by the transition of releasing sites to refractory sites and the recovery of refractory sites to releasable sites:

$$\frac{dZ}{dt} = \frac{Y}{\tau_{in}} - k_{rec} \cdot Z \tag{5}$$

Short-term facilitation

Facilitation of release is hypothesized to be caused by a number of presynaptic Ca^{2+} related mechanisms, including increased Ca^{2+} influx, Ca^{2+} buffer saturation, and high-affinity Ca^{2+} sensors level (Regehr, 2012; Jackman et al., 2016). Therefore, the facilitation is simulated as a Ca^{2+} dependent process. The enhanced Pr is determined by the facilitation and the initial release probability per release site (P_0) as given by Felmy et al., (2003) and Trommershäuser et al. (2003):

$$P_r = \frac{1 - P_0}{1 + \left({}^{Kf}/_{Ca}\right)^{nf}} + P_0 \tag{6}$$

where K_f is the dissociation constant for Ca^{2+}-bound molecules and nf is the Hill coefficient. P_r is in the range of P_0 to 1.

Proposed hypothesis of postsynaptic response: quantal release, one release site, and one vesicle

A 'quanta' of neurotransmitters, corresponding to a single vesicle of neurotransmitters, evokes a mEPSC and the EPSC evoked by a single AP is in multiples of mEPSC (del Castillo and Katz, 1954). The mean amplitude of the postsynaptic EPSC in a CA1 neuron following an AP is described by a binomial model (Silver, 2003):

$$EPSC = N \cdot P \cdot Q \tag{7}$$

where *P* is the release probability over the population of release sites, and *Q* is the mean amplitude of their miniature ESPCs. The underlying assumption for this simple interpretation of postsynaptic ESPCs is that *P* and *Q* are both uniform across the contributing release sites (Silver, 2003). *P* is determined by the mean release probability and the availability of releasable sites, thus, $P = P_r \cdot X$.

Normalization of responses

The facilitation ratio is experimentally measured by dividing the amplitude of the following ESPC by the amplitude of the first ESPC. Therefore, in our study, we define the normalized responses as the amplitudes of corresponding ESPCs evoked by multiple action potentials in succession normalized by the amplitude of the ESPC evoked by the first action potential as given by:

$${Response_M}/{Response_1} = \frac{EPSC_M}{EPSC_1} = \frac{N_M \cdot P_{r,M} \cdot X_M \cdot Q_M}{N_1 \cdot P_{r,1} \cdot X_1 \cdot Q_1} \tag{8}$$

where $EPSC_M$ is the amplitude of the EPSC evoked by the M^{th} action potential, N_M, $P_{r,M}$, X_M and Q_M are the number of the release sites, the mean release probability of release

sites, the mean availability of release sites, and the mean amplitude of mEPSC at the Mth AP, respectively. Further assumptions are taken to simplify equation (8) into equation (9): (1) the facilitation and depression are both absent ($P_{r,1} = P_0$ and $X_1=1$) before the first action potential (Ca_{res} is at rest); and (2) the number of release sites and their mean amplitude of mEPSC remain unchanged during the multiple action potentials applied in a short time window, as given by:

$$Response_M / Response_1 = \frac{P_{r,M} \cdot X_M}{P_0} \quad (9)$$

The pair-pulse ratio (PPR) is a special case where the second response is normalized:

$$PPR = \frac{Response_2}{Response_1} = \frac{P_{r,2} \cdot X_2}{P_0} \quad (10)$$

Parameter estimation

Parameters are estimated using Markov Chain Monte Carlo (MCMC) method using MCMC toolbox of Matlab (Haario et al., 2006). (The MCMC toolbox can be downloaded from this site: http://helios.fmi.fi/~lainema/mcmc/). Two sets of parameters, corresponding to wide type and Syt7 KO conditions, respectively, are obtained by minimizing the sum of two squared errors wild type and Syt7 KO between normalized model outputs (given by equation (9)) and experimental data. The experimental data was obtained from a study by Jackman et al. (2016), where responses following 10 stimuli, at four frequencies (5, 10, 20 and 50 Hz), are provided and normalized by the first response. Data sets were obtained from mice in each group (wide type *vs*. Syt7 knock out), and there were significant differences in peak PPR and response10/response1 between wide type and Syt7 knockout mice at all synapses over all 4 frequencies ($P < 0.01$; Student's *t*-test). Since normalized response for Syt7 knockout was much weaker than that for wide type mice (P value < 0.01), a weight is assigned to the squared error of Syt7 knockout to balance the contribution of two errors to the total error. The common parameters, which are related to the processes unaltered by Syt7 knockout, are conserved between wide-type and Syt7 knock out sets. According to Jackman et al. (2016), values of P_0, k_0 and Ca^{2+}-related parameters, K_{ca} and τ_{ca}, are unaltered between wide-type and knockout conditions. Other parameters have two separate copies, one for wide-type and the other for Syt7 knockout, and are trained separately. During the estimation, each iteration performs two pieces of training, one against wide-type data followed by the other against Syt7 knockout data. Both trainings estimate common parameters, and wide-type training/Syt7 knockout training estimate wide-type/Syt7 knockout copies, respectively. The training is stopped when parameters are converged.

Statistical analysis

This model was programmed using MATLAB (Ver. R2016a; Mathworks Inc., Natick, Massachusetts, USA). Source code was available in ModelDB (McDougal et al., 2017) at http://modeldb.yale.edu/239066.

Results

In this section, we provide the results related to the factors regulating short-term synaptic plasticity and to highlight critical behavior differences between wide-type and Syt7 knockout to support our later discussions.

General model overview

The general model includes three major processes: (1) presynaptic Ca^{2+} dynamics, (2) short-term plasticity, and (3) postsynaptic response. The presynaptic Ca^{2+} dynamics are simulated with presynaptic action potentials at different frequencies as inputs. The facilitation and depression for a synapse are Ca^{2+}-dependent and they modulate the release of neurotransmitter in response to a presynaptic action potential. There are three states for a synapse: releasable, releasing and refractory states. The state transitions are in a cyclic fashion as shown in **Figure 1A1**. A synapse is capable to release a vesicle after a presynaptic action potential only when it is in the releasable state, and the release probability is modulated by the short-term plasticity. The postsynaptic response is evaluated according to the quantal release hypothesis (del Castillo and Katz, 1954). In SC, neurons are connected by a larger number of synaptic contacts and each contact contains one release site (Branco and Staras, 2009; Bliss and Collingridge, 2013). The exact releasing profile of these contacts in central neurons is unclear. We assume that there are N contacts/sites in our system excluding silent synapses. All release sites are independent and each one of them has one vesicle ready to be released. Hence, a release site releases one-or-none 'quanta' unit per action potential. The model selection is based on the consideration of model structure as previously reported (Dittman et al., 2000; Sun et al., 2005) and information provided in the given data (see **Additional file 1** including **Additional Figure 1** for explanation).

Non-uniform release probability model

Previous models were developed according to a binomial model with N release sites and the uniform mean release probability of release sites, P_r (**Figure 1A1**, one-population model, abbreviated as 1P model, see the Methods section). The 1P model partially captures the experimental observations. The depression during the first few stimuli of Syt7 knockout predicted by the 1P model is far from the great depression as seen in experimental observations (**Figure 1A2**) (Jackman et al., 2016). The 1P model does not capture the 'gap' between wide-type and Syt7 knockout during the first few stimuli; the 1P model follows either the great facilitation in wide-type or the great depression in Syt7 knockout, but not both.

There are two possibilities for the 'gap': (1) the release sites have non-uniform release probabilities (Walmsley et al., 1988; Rosenmund et al., 1993; Silver, 2003; Trommershäuser et al., 2003). The minority of release sites have a high P_r and are depleted by the first action potential, and the majority of release sites have a much lower P_r and produce significantly weaker EPSC following the subsequent action potential; and (2) another source of depression exists in addition to the de-

pletion of release sites. For example, use-dependent depression (Catterall and Few, 2008) and inactivation of calcium channels (Mochida et al., 2008) change the Ca^{2+} influx. Here, we focus on the first possibility for the following reasons: (1) no significant change of total Ca^{2+} influx between two closely applied stimuli was detected for the given data (Jackman et al., 2016). Hence, the latter possibility would only occur, if it does occur, at the subset of Ca^{2+} channels that trigger neurotransmitter release; and (2) for the latter possibility, the depression often occurs following the prolonged high-frequency stimulation (Regehr, 2012), but the depression as seen in the Syt7 knockout response (**Figure 1A2**) is great at the second stimulus. Hence, the latter possibility contributes less to the great depression in Syt7 knockout, at least for the first 10 stimuli.

We develop the simplest non-uniform release probability model (**Figure 1B**, two-population model, abbreviated as 2P model) based on additional assumptions from the A1 model: (1) there are two sets of release sites, the majority, $N(1\text{-}P_H)$ sites, have a low mean initial release probability (P_0) and the rest, $N{\cdot}P_H$ sites, have a much higher P_0. P_H denotes the fraction of high P_0 release sites (high sites). Pr has a range between 0 and 1 and is given by the sum of P_0 and the facilitation, which is controlled by Ca_{res} and increases the release probability following action potential (Dobrunz and Stevens, 1997; Murthy et al., 1997). The releasable fractions of the two sets are denoted by X_1 (high sites) and X_2 (low sites) given the initial values of P_H and $1–P_H$, respectively, at rest; (2) the depression process, the facilitation process and miniature EPSCs (mEPSC with a mean amplitude Q) are the same across the two sets; (3) both sets follow the binomial model so that the overall mean EPSC amplitude is $N{\cdot}Q(P_{r1}{\cdot}X_1 + P_{r2}{\cdot}X_2)$; and (4) P_H is conserved between wide-type and Syt7 knockout.

As shown in **Figure 2**, the 2P model has a good agreement with the 'gap' and the general trends over different frequencies. The values for P_0 predicted are differed by more than 10 folds; the majority of release sites (83%) have a low P_0 of approximately 0.03 and the rest (17%) have a high P_0 of approximately 0.55.

The difference between parameters highlights possible roles of Syt7

Although the estimated parameters of the 2P model (**Table 1**) may not contain useful quantitative information for the processes governing releasing and plasticity primarily due to the great reduction in the synaptic processes and the uncertainties in the feasible ranges of parameters, the estimated parameters contain useful relative information between wide-type and Syt7 knockout as well as agree well with the general trends of synaptic vesicle releasing. Those bases are adequate and sufficient for our purpose to investigate the dynamic behavioral differences between wide-type and Syt7 knockout to understand the functional importance of short-term plasticity.

The differences of parameters between Syt7 knockout and wide-type are summarized: (1) the maximum fast recovery rate is significantly reduced, but a much smaller Ca^{2+} rise is required to reach the maximum rate (**Figure 3A**). This result indicates that the fast recovery rate has at least two components: one moderate rate responses fast to Ca^{2+} rise and a Syt7 controlled fast rate which requires a higher Ca^{2+} rise to activate. The higher Ca^{2+} rise may be accumulated by a large number of stimuli. A previous experimental study shows that Syt7 knockout causes a significant reduction in the fast replenishment rate of synaptic vesicles following the prolonged high-frequency stimulation while a minor change of the responses following a small number of stimuli (Liu et al., 2014). This yields consistency with our simulation results; (2) the facilitation is significantly reduced but is not completely eliminated (**Figure 3B**), which again yields consistency with the experimental observation where a small facilitation is observed when P_0 is reduced significantly by decreasing the extracellular Ca^{2+} level (Jackman et al., 2016); (3) the relationship between Ca^{2+} elevation and Pr is linear for a moderate Ca^{2+} elevation (≤ 2 normalized calcium level (*norm. Ca*)), and Pr approaches a plateau with the greater Ca^{2+} elevation (> 2 *norm. Ca*); and (4) the difference in Pr between the two sets of release sites reduces while Ca^{2+} level increases in wide type, but the difference only reduces by a small amount in Syt7 knockout (**Figure 3B**). In other words, the facilitation

Table 1 Parameter sets for WT and KO conditions of two-population model (2P model)

Parameter	Biological meaning	WT	Syt7 KO
τ_{ca}	Decay time constant for Ca^{2+}	0.0301 ms	0.0301 ms
K_{ca}	Dissociation constant for Ca^{2+} decay	1.19	1.19
k_0	The basal recovery rate	0.9/ ms	0.9/ms
k_{max}	Faster recovery rate	26/ms	8.25/ms
K_r	Dissociation constant for recovery	4.05	0.65
n_r	Hill coefficient for recovery	1	3.92
τ_{in}	Time constant for the transition into refractory states	0.003 ms	0.003 ms
K_f	Dissociation constant for Ca^{2+}-bound molecules	2.4	19.4
n_f	Hill coefficient for facilitation	1.15	1.5
P_H	Fraction of high P0 release sites (high sites)	0.17	0.17

WT: Wild-type; Syt7: synaptotagmin 7; KO: knockout.

'activates' the low P_0 release sites and Syt7 knockout lacks this capability. The consistency of the model outputs against experimental observations assures the believability of the estimated parameters for our latter investigations.

Selective alteration of PPR by KO

The PPR is the ratio of the second response to the first response evoked by two closely spaced action potentials. PPR reflects the short-term changes of the postsynaptic response as a result of the dynamic modulations by the short-term facilitation and depression. PPR of 1 denotes the balance between the facilitation and depression, while greater or less than 1 denotes the dominance of the facilitation or the depression, respectively. The conditions for the switching between the facilitation and the depression are not clear (Dobrunz and Stevens, 1997). We test the relationship between PPR and several factors including P_H, P_0 of the high sites and the inter-action potential interval.

The short-term change lasts for less than 1 second and the degree of the change increases as the inter-action potential interval decreases (**Figure 4**). For an inter-action potential interval of 10 seconds, PPR is at a steady level at 1, indicating a complete recovery from any short-term changes (**Figure 4**). But for an inter-action potential interval of 1 second, PPR is slightly above 1 for low P_H level and high P_0 level (**Figure 4**), indicating signs of a weak facilitation which produces significant short-term changes only at low P_r level. These results suggest that the majority of the response for large inter-action potential intervals is contributed by the minority of high sites because the facilitation is weak leading to a negligible release probability for the majority of low P_0 release sites (low sites). Correspondingly, for small inter-action potential intervals, the first response is contributed by the minority of high sites and the second response is contributed by the majority of low sites due to the strong facilitation. Furthermore, the switching between the facilitation and the depression depends on P_H and high P_0; increasing P_H or high P_0 shifts the balance towards the depression since more release sites are depleted by the first action potential (**Figure 4**). Therefore, the balance between the facilitation and the depression requires a proper coordination between P_H and high P_0. As for the 0.01 second inter-action potential interval, the balance requires at least the moderate levels of both P_H and high P_0 to cause sufficient depletion by the first AP to offset the strong facilitation at the second action potential (**Additional Figure 2**). But, for large inter-action potential intervals, the requirements of the depletion are much less since the facilitation is much weaker (**Additional Figures 3** and **4**). Alternatively, the inter-action potential interval can be decoded by a proper coordination between P_H and high P_0 where the postsynaptic response is constant over stimuli.

The PPR difference is the difference between the PPRs of wide-type and of Syt7 knock out. The difference is very small (close to 0) at the 10-second inter-action potential interval, indicating an insignificant role for Syt7 in largely separated action potentials, i.e., the basal transmission (**Figure 5**). The difference increases as the inter-action potential interval decreases (**Figure 5**). For intervals smaller than 1 second, the PPR difference follows a decreasing trend as P_H (**Figure 5A**) or high P_0 increase (**Figure 5B**). These general behaviors of the difference occur because of the decrease in PPR by increasing depression as a result of the relationships between PPR and P_H, high P_0 and inter-action potential interval, as discussed previously, with Syt7 playing a minor role in these behaviors. However, at the 1 second inter-action potential interval, the difference decreases rapidly before reaching a steady level (**Figure 5**). This result is expected because the high sites dominate the response at large inter-AP intervals. Since the facilitation has insignificant contribution to high sites at large inter-action potential intervals (**Figure 4**), the PPR difference approaches to a steady level with the increase of either the portion or P_0 of high sites. Once the steady level is reached, the reduction in response by Syt7 knock out is mostly contributed by high sites. On the other hand, at the 0.01 second inter-action potential interval, the set of low sites maintains a considerable contribution to the PPR difference when the portion of high sites increases as indicated by the decreasing line (**Figure 5** and **Additional Figure 5**). These results yield interesting information that the degree of reduction caused by Syt7 knockout takes two factors into account: the type of release sites and the inter-action potential interval. The majority of the reduction occurs on high sites or low sites for large or small inter-action potential intervals, respectively. However, the selection is not simply a function of Syt7 but also originates from the non-uniform releasing structure of the release sites.

Selective alteration of multiple-AP stimulations by KO

Sustained presynaptic stimulation, depending on the frequency of stimulation, can produce a long-lasting depression which recovers slowly or long-lasting synaptic enhancement (Regehr, 2012). Besides, non-uniform release probability is suggested to affect the synaptic strength especially when long-lasting synaptic enhancement is induced by different stimulation patterns (Rosenmund et al., 1993). Syt7 has shown to contribute significantly to the short-term changes in the second of two closely spaced APs without affecting the first response; the reduction in Syt7 KO is dependent on release site and inter-AP intervals. However, the prolonged stimulations induce greater changes in postsynaptic response, as compared to that of PPR, by accumulating more Ca_{res} for the greater facilitation and depleting more release sites before the full recovery. The nature of relationship among Syt7, the release site and the inter-AP interval still holds for more realistic multiple-AP stimulations environment can suggest a possible role of short-term plasticity in the synapse.

To better reflect the input specificity, we normalize EPSC amplitude of a set of release site by their max EPSC amplitude as given by:

$$Norm.\ Response_M = \frac{EPSC_M}{max\ EPSC} = \frac{N \cdot P_H \cdot P_{r1,M} \cdot X_{1,M} \cdot Q}{N \cdot P_H \cdot Q} = P_{r1,M} \cdot X_{1,M} \quad (11)$$

where, $P_{r1,M}$ and $X_{1,M}$ are mean release probability and

mean availability of high sites at the M^{th} AP, respectively. As shown, the normalized response is the same to the average release probability of the corresponding set of release sites. This measure reflects the average behavior of a single release site.

Since low-frequency stimulation (100 action potentials applied in 1Hz) and high-frequency stimulation (100 action potentials applied in 100 Hz) are common protocols for triggering long-term synaptic plasticity in SC, the behaviors of 2P model in response to the two stimulations are tested. During first 10 action potentials of low-frequency stimulation, Syt7 knockout causes a significant reduction of the normalized response in only the high sites (**Figure 6A**). During the first 10 action potentials of high frequency stimulation, both sites show reductions (**Figure 6B**). But the reduction in high sites is minor before the 5th stimuli and becomes significant afterwards, when the fast recovery by Syt7 is switched on. On the other hand, the reduction is always significant for the low sites, especially during first 6 stimuli. These results suggest the selectivity of Syt7 on release site during prolonged stimuli.

However, long-term synaptic plasticity at a single synaptic contact relies on the sustained release to build-up the postsynaptic Ca^{2+} level (Bliss and Collingridge, 1993). In this case, the average release profiles across the 100 action potentials of low frequency stimulation are more important. We calculate the average normalized response and a significant reduction in the average normalized response is revealed in Syt7 knockout only for the large P_0 (> 0.5) during low frequency stimulation (**Figure 7A**). In high frequency stimulation, there is a significant reduction in Syt7 knockout for the whole range of P_0 (**Figure 7B**). However, the average normalized response in wide type is similar across the whole range of P_0 while that in Syt7 knockout exhibits a great drop approaching the low side of P_0 (**Figure 7B**). Given that the exact threshold and mechanism of postsynaptic response are unclear, if the postsynaptic response to multiple-action potential stimulations is strongly linked to the presynaptic release profile, then we can expect Syt7 knockout to cause a reduced postsynaptic response and synaptic strength.

Discussion

In this study, we use a mathematical model to study the possible role of Syt7 and its driven short-term synaptic plasticity in the synapse, as well as the possible connection between presynaptic release and postsynaptic response. We observe using a mathematical model that release sites have non-uniform release probability in SC and different release sites contribute differently to transmission and plasticity. Having these properties, synaptic plasticity may function as a high-pass filter. But, to be able to adapt these release sites, a selection process is required to select the appropriate release sites and train them with respect to a target frequency for the filter and Syt7 may be involved.

Short-term plasticity as a high-pass filter

We show a hypothesized system that short-term synaptic plasticity can function as a high-pass filter (Rothman et al., 2009), which allows the signals with a frequency higher than a threshold to trigger a postsynaptic action potential. We also show that Syt7 helps to train the target frequency of the filter through modulations on the selected release sites.

As shown in **Figure 4**, the balance of facilitation and depression requires the proper coordination between the inter-action potential interval and the release probability. Hence, for carefully trained release probability, the target inter-action potential interval is right on the balance between facilitation and depression. The dominance in the facilitation or the depression indicates a smaller or a larger interval to the target, respectively. However, the basal transmission is not affected since it is fully recovered from facilitation and depression. Setting a threshold of postsynaptic potential at the basal transmission to generate an action potential would only allow the higher frequency burst (smaller action potential interval) and filter out the low-frequency burst.

Figure 8 shows an example of a high-pass filter with a target inter-action potential interval of 50 ms. Both uniform and non-uniform models can help distinguish smaller and larger inter-action potential intervals. But the PPR difference in the uniform model is rather small which may be difficult to be detected in a postsynaptic neuron. The non-uniform model shows a significant PPR differences in both smaller and larger intervals. The reason is that the uniform model requires a high P_0 to induce sufficient depression to balance the strong facilitation. But a high P_0 diminishes the potential for the facilitation as well as the availability of release sites for the next responses. The non-uniform model does not have this problem as the depression mainly results from the minority of high sites that will leave sufficient potential for the facilitation by the low sites. Hence, by a proper coordination of P_H and high P_0, the balance can be reached without having to deplete release sites too much. Furthermore, the amplitude of mEPSC may be non-uniform (Silver, 2003) that may add another dimension of adaptability to have an even higher degree of differentiation for the high-pass filter.

Activity-dependent selection of release sites

However, a training process is required to selectively train release sites to adapt to the target inter-action potential interval. Based on our results, we propose a hypothesized system that Syt7 selects release sites according to the presynaptic stimulation frequency and the expression of Syt7 in target sites may be a tag to direct the site to enhance postsynaptic response and modulate synaptic strength (**Figure 9**).

Syt7 knockout causes reduction in PPR, but not in basal transmission (**Figure 5**). However, the reduction is on high sites at the large inter-action potential intervals because the depletion in these sites is difficult to be recovered by the reduced fast recovery rate of Syt7 knockout within these intervals. On the other hand, the majority of the reduction is on low P_0 release sites at small inter-action potential intervals because the lack of facilitation significantly reduces the response of these sites.

Over the first 10 action potentials of low frequency stimu-

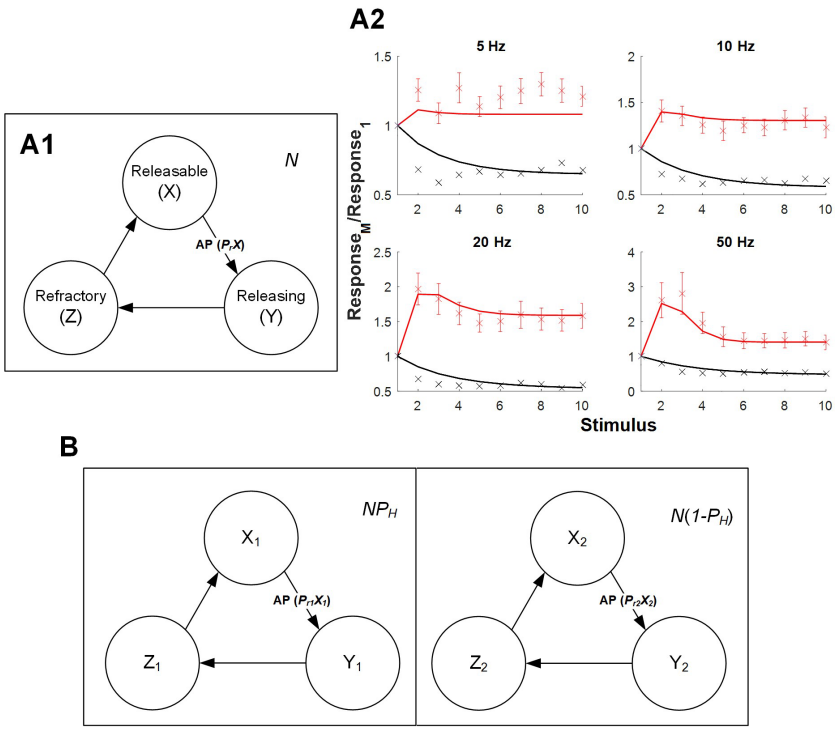

Figure 1 Models of presynaptic release.
Red crosses with error bars are wide-type (WT) data and black crosses are knockout (KO) data. Black and red lines are corresponding simulation results. Data are retrieved from Extended Data Figure 4 in Jackman et al. (2016). (A1) The uniform one-population model (1P model) with N release sites and uniform P_r (see Methods for details). Release sites have three possible states: releasable sites, releasing sites, and refractory sites, using X, Y and Z to denote the average fractions of sites at these three states, respectively. Action potential causes releasable release sites (or $P_r{\cdot}X$ in terms of the fraction) to release and enter into a brief releasing state. After releasing, the sites become refractory and undergo a very slow recovery process to become releasable. Ca_{res} is determined to accelerate this recovery process (Dittman and Regehr, 1998; Liu et al., 2014). The mean amplitude of EPSC is calculated by $N{\cdot}P_r{\cdot}X{\cdot}Q$, where Q is the mean amplitude of mEPSC induced by a quanta of neurotransmitters. (A2) After parameter estimation (see Methods for the procedure), the 1P model captures the trends of WT data. However, a significant mismatch is revealed for the first few stimuli in Syt7 KO data. (B) Non-uniform two-population model (2P model). Release sites are divided into two binomial models that one model with $N{\cdot}P_H$ release sites and a very high uniform P_r, P_{r1}, and the other model with N(1–PH) release sites and a low uniform P_r, P_{r2}. N: Total release sites; X, X_1, X_2: releasable sites; Y, Y_1, Y_2: releasing sites; Z, Z_1, Z_2: refractory sites; P_r: uniform release probability; P_{r1}: high uniform release probability; P_{r2}: low uniform release probability; PH: fraction of release sites with high initial release probability; AP: action potential. $Response_M/Response_1$: normalized responses (see Eq. (9)).

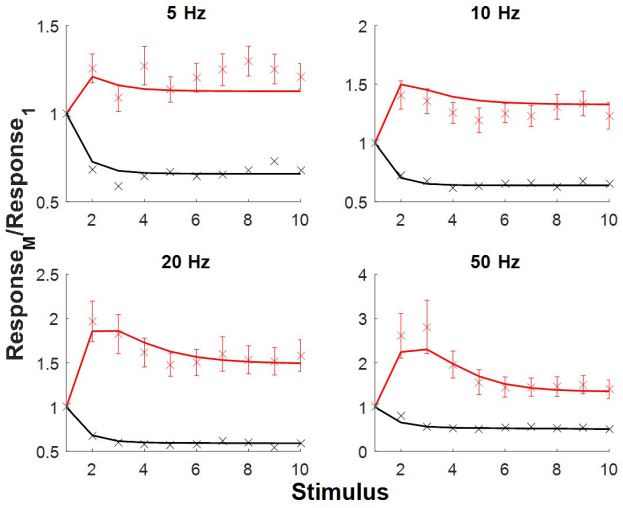

Figure 2 After parameter estimation, two-population model (2P model) in Figure 1B captures the trends of both wild-type (WT) and Syt7 knock out (KO) data (retrieved from Extended Data Figure 4 in Jackman et al. (2016)).
Red crosses with error bars are WT data and black crosses are KO data. Black and red lines are corresponding simulation results. $Response_M/Response_1$: normalized responses (see Eq. (9)).

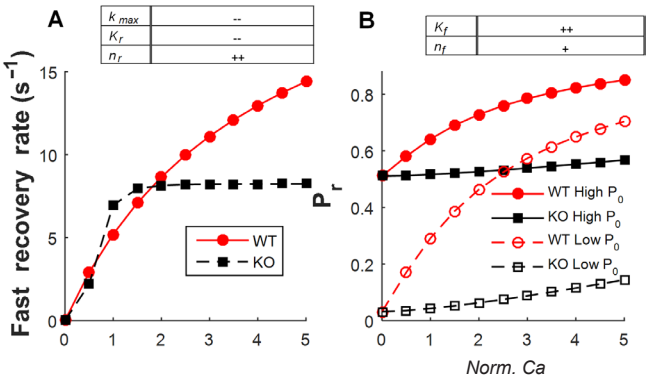

Figure 3 The difference in parameters governing the wild-type (WT) and Syt7 knockout (KO) responses.
Both the recovery and facilitation are controlled by the normalized calcium level (Norm. Ca), and are modeled by Hill equations carrying three parameters: max recovery rate or facilitation, dissociation constant and the Hill coefficient. (A) The change in the fast recovery rates between WT and KO. The table above summarizes the quantitative changes in KO parameters, related to the recovery from depression, from that of WT. –, + and/denote decrease, increase and no change, respectively. Repeats denote a significant change. (B) The change in the facilitation between WT and KO as well as between the two sets of release sites. The max facilitation is 1. The table above summarizes the quantitative changes in KO parameters, related to the facilitation, from that of WT. $P_r = P_0$ when normalized calcium level is 0 (at rest). k_{max}: Faster recovery rate; K_r: dissociation constant for recovery; n_r: Hill coefficient for recovery; K_f: dissociation constant for Ca^{2+}-bound molecules; n_f: hill coefficient for facilitation; P_r: uniform release probability; P_0: initial release probability.

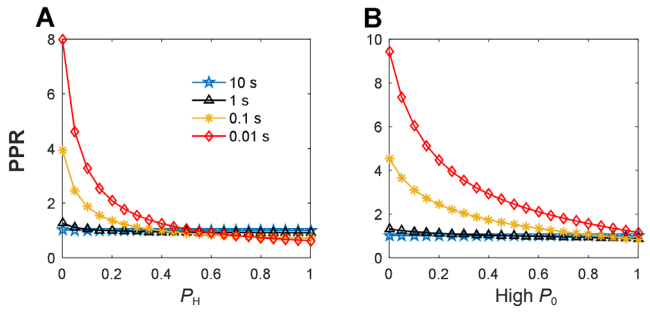

Figure 4 PPR dependence on P_H, P_0 and the inter-AP interval in wild-type condition.
(A) PPR as a function of P_H (0 –1) and inter-AP interval (10, 1, 0.1, and 0.01 seconds). (B) PPR as a function of high P_0 (0 –1) and inter-AP interval (10, 1, 0.1, and 0.01 seconds). Other parameters are held at their estimated levels. AP: Action potential; PPR: pair-pulse ratio; P_H: fraction of release sites with high initial release probability; P_0: initial release probability.

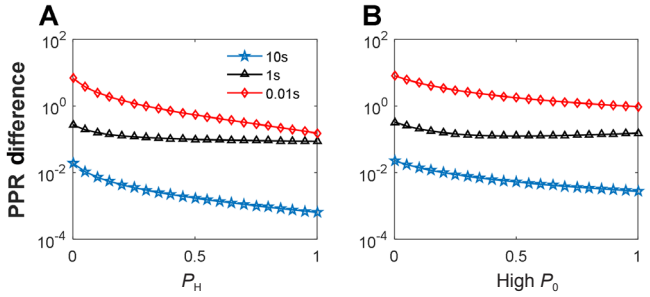

Figure 5 PPR difference between wild-type (WT) and synaptotagmin 7 (Syt7) knockout (KO).
PPR difference is calculated by PPR of WT–PPR of KO. (A) PPR difference (log scale) as a function of P_H (0–1) and inter-AP interval (10, 1, and 0.01 seconds). (B) PPR difference (log scale) as a function of the high P_0 (0–1) and inter-AP interval (10, 1, and 0.01 seconds). Other parameters are held at their estimated levels. AP: Action potential; PPR: pair-pulse ratio; P_H: fraction of release sites with high initial release probability; P_0: initial release probability.

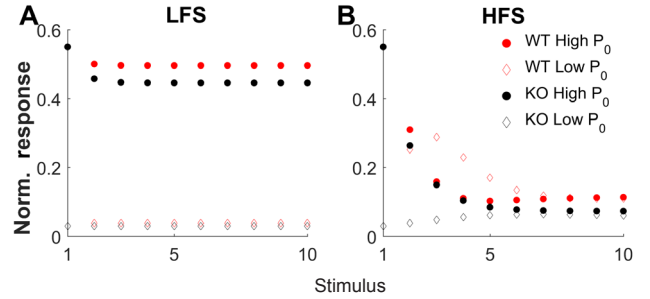

Figure 6 Normalized response of the release sites during the first 10 stimuli of low-frequency stimulation (LFS) and high-frequency stimulation (HFS).
The normalized response (Norm. Response) of two different sets (high sites and low sites) of release sites in both wild-type (WT) and synaptotagmin 7 (Syt7) knockout (KO) during (A) LFS and (B) HFS. Norm. Response is calculated by Eq. (9). P_0: Initial release probability.

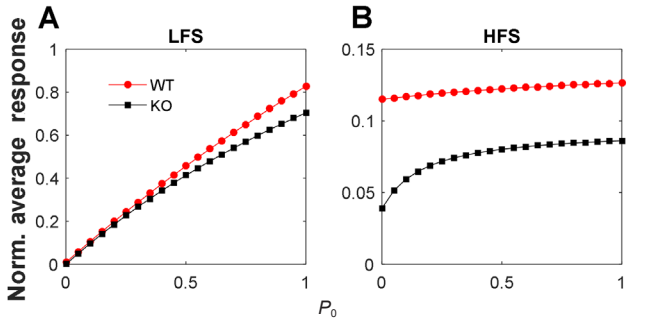

Figure 7 Normalized average response of the release sites across the 100 APs of low-frequency stimulation (LFS) and high-frequency stimulation (HFS).
The normalized average response (Norm. average response) of the release sites (high sites and low sites) with different P_0 in both wild-type (WT) and synaptotagmin 7 (Syt7) knockout (KO) during (A) LFS and (B) HFS. AP: Action potential; P_0: initial release probability.

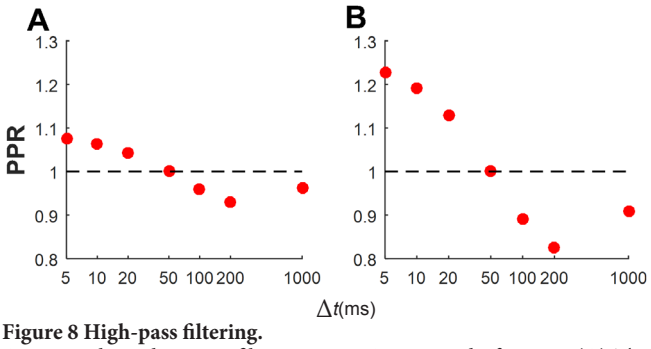

Figure 8 High-pass filtering.
An example is shown to filter an inter-AP interval of 50 ms. (A) The filter is based on a uniform release probability model (P_H = 1, high P_0 = 0.313). (B) The filter is based on a non-uniform release probability model (P_H = 0.2225, high P_0 = 0.8, and low P_0 = 0.03). PPR: Pair-pulse ratio; P_H: fraction of release sites with high initial release probability; P_0: initial release probability.

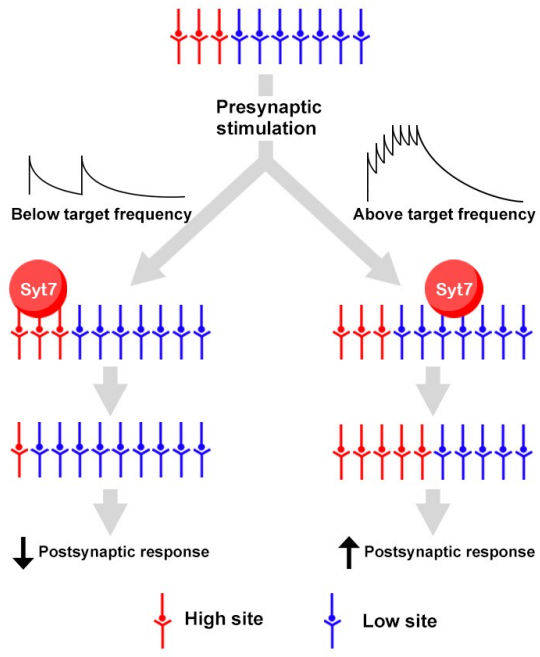

Figure 9 Schematic representation of the hypotheses proposed for activity-dependent selection of release sites by synaptotagmin 7 (Syt7).
When presynaptic stimulation frequency is below the target frequency, Syt7 controls the high sites to reduce postsynaptic response. Otherwise, Syt7 controls the low sites to increase postsynaptic response.

lation, Syt7 knockout reduces the responses of the high sites while the low sites remain unchanged (**Figure 6A**). As for high frequency stimulation, the responses of the high sites are similar between wide type and Syt7 knockout before the 5th action potential and are slightly different afterwards (**Figure 6B**). The low sites display a significant difference before the 6th action potential and the difference becomes smaller afterwards (**Figure 6B**). Responses reach a steady level after the 7th action potential in high frequency stimulation. The steady levels are similar between two sets of release sites in wide type, while the levels are slightly different in Syt7 knockout.

Syt7 knockout causes reductions in average responses across the 100 action potentials during high frequency stimulation and low frequency stimulation (**Figure 7**). Similarly, the reduction is on the high sites during low frequency stimulation and the low sites reveal a greater reduction than the high sites during high frequency stimulation.

All these results suggest that Syt7, together with the non-uniform release structure, is a candidate to control the long-term changes (for example, long-term potentiation and long-term depression) which are induced by multi-action potential stimulations. The Syt7 knockout causes consistent alterations across the PPR, the first 10 responses and the average response. In low frequency stimulation, Syt7 controls the high sites to reduce postsynaptic response and synaptic strength. In high frequency stimulation, Syt7 controls the low sites to increase postsynaptic response and synaptic strength. If the reduction and increase cause changes in P_H by changing the ratio of high sites to low sites, i.e., through activation of silent synapses and inactivation of synapses to be silent (Isaac et al., 1995), or changes the P_0 of high sites by presynaptic mechanisms (Regehr, 2012), then we have a theoretical basis for the high-pass filter as well as the regulation of the target of the filter (**Figure 9**).

Limitations

The current work has a number of limitations: (1) The previous experimental study (Felmy et al., 2003) states that there is a supralinear relationship between the facilitation and Ca^{2+} pre-elevation, however, we predict a linear relationship between the presynaptic release probability and moderate Ca^{2+} elevation. Hence, postsynaptic parameters and mechanisms, which we didnot consider in this study, are likely to contribute to facilitation: for example, the EPSC dynamics, the non-uniform nature of mEPSC and postsynaptic receptor desensitisation and saturation; (2) transient activation and inactivation of release sites are not considered; and (3) depletion of vesicle pools and different rates of vesicle pool depletion are ignored. These processes may cause large changes to postsynaptic responses during a large number of continuous stimuli, for example, high frequency stimulation. It is important to conduct Syt7 wide type and knockout experiments further on different types of synapses to obtain more data for parameter estimation to test the proposed hypotheses in this study. In the future, with more knowledge of the mechanisms across the synapse, a new mechanistically driven model can be developed to incorporate pre- and post-processes, so that a comprehensive understanding of the relationship between synaptic plasticity and synaptic functions can be obtained. Understanding of the relationships is essential to deduce the casual relationships between brain diseases and synaptic malfunctions.

Author contributions: *YH and DK developed the models with the assistance from JL and all three authors contributed to writing and editing of the paper and approved the final version of the paper.*
Conflicts of interest: *None declared.*
Financial support: *This work was supported by a grant from Lincoln University, New Zealand. The funding body played no role in the study design, in the collection, analysis and interpretation of data, in the writing of the paper, and in the decision to submit the paper for publication.*

Data sharing statement: *Datasets analyzed during the current study are available from the corresponding author on reasonable request.*
Plagiarism check: *Checked twice by iThenticate.*
Peer review: *Externally peer reviewed.*

Open peer reviewer: *Rodolfo Gabriel Gatto, University of Illinois at Chicago, USA.*

Additional files:

Additional Figure 1: *Pair-pulse ratios (PPRs) across wild-type (WT) and Syt7 knockout (KO) neurons.*
Additional Figure 2: *Pair-pulse ratios (PPRs) at 0.01 second inter-action potential interval as a function of PH and high P0.*
Additional Figure 3: *Pair-pulse ratios (PPRs) at 0.1 second inter-action potential interval as a function of PH and high P0.*
Additional Figure 4: *Pair-pulse ratios (PPRs) at 1 second inter-action potential interval as a function of PH and high P0.*
Additional Figure 5: *Pair-pulse ratios (PPRs) between wild-type (WT) and Syt7 knockout (KO) condition.*
Additional file 1: *Processes to be included in the model.*
Additional file 2: *Open peer review report 1.*

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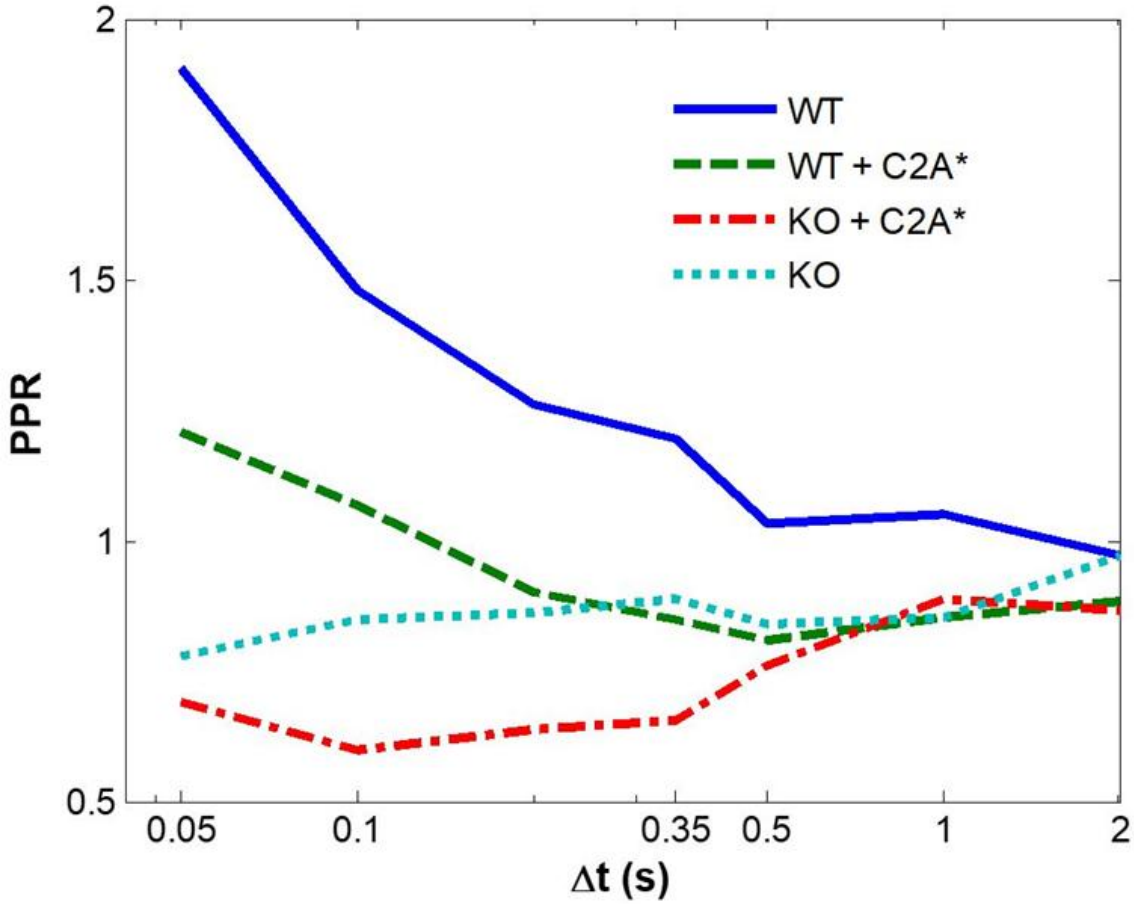
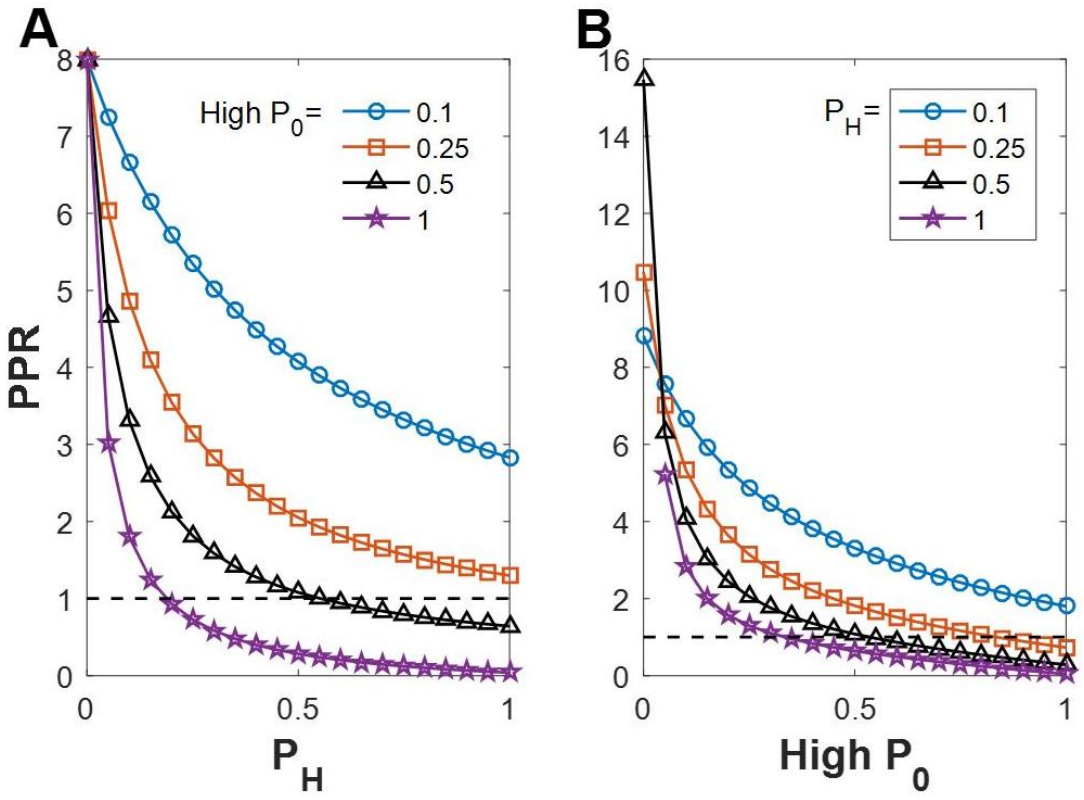
P-Reviewer: Gatto RG; C-Editor: Zhao M; S-Editor: Li CH; L-Editor: Song LP; T-Editor: Liu XL



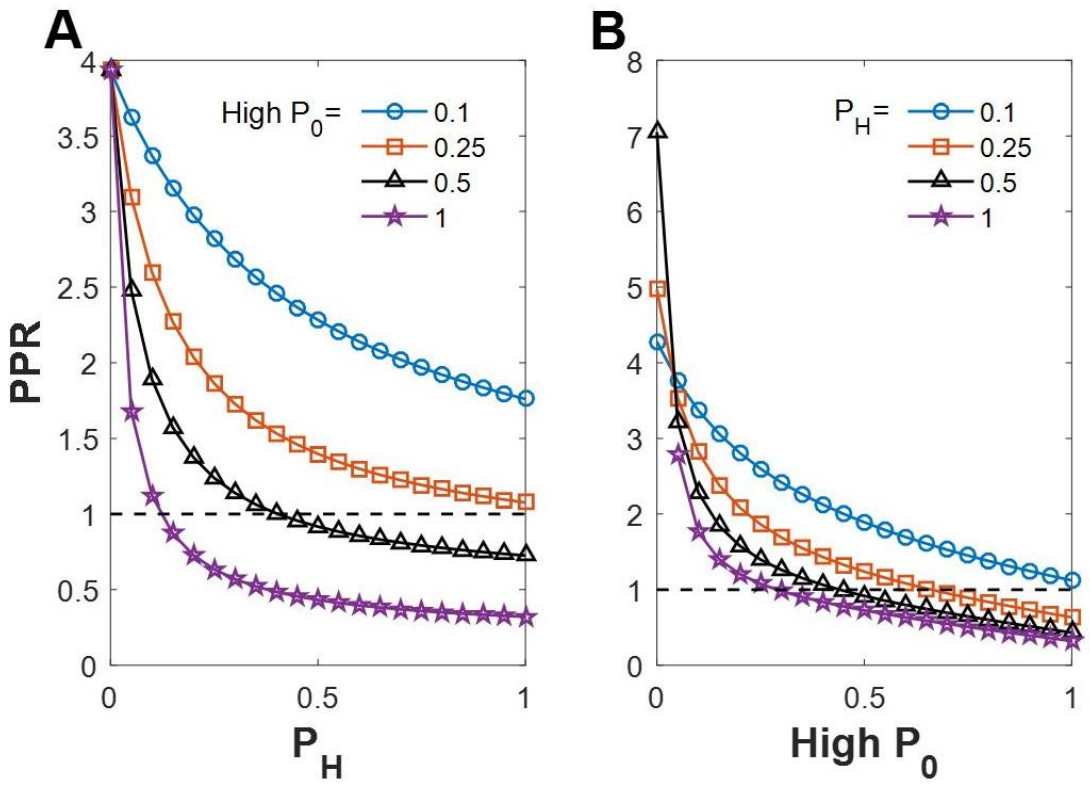
Additional Figure 1 Pair-pulse ratios (PPRs) across wild-type (WT) and Syt7 knockout (KO) neurons.

Experimental data are retrieved from Jackman et al. (2016). $C2A^{*}$ is a mutated Ca^{2+}-insensitive C2A domain. Only WT expresses the strong facilitation, while the other three express the reduced or impaired facilitation. Δt is the time interval between two closely spaced action potentials.

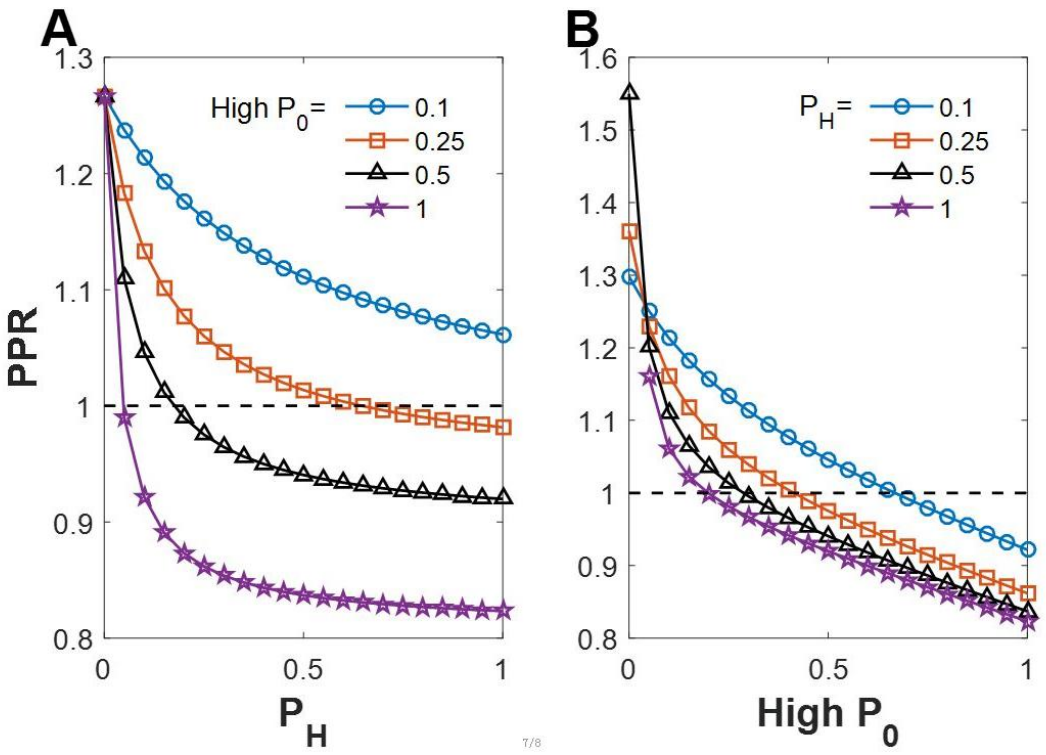


Additional Figure 2 Pair-pulse ratios (PPRs) at 0.01 second inter-action potential interval as a function of P_H and high P_0.

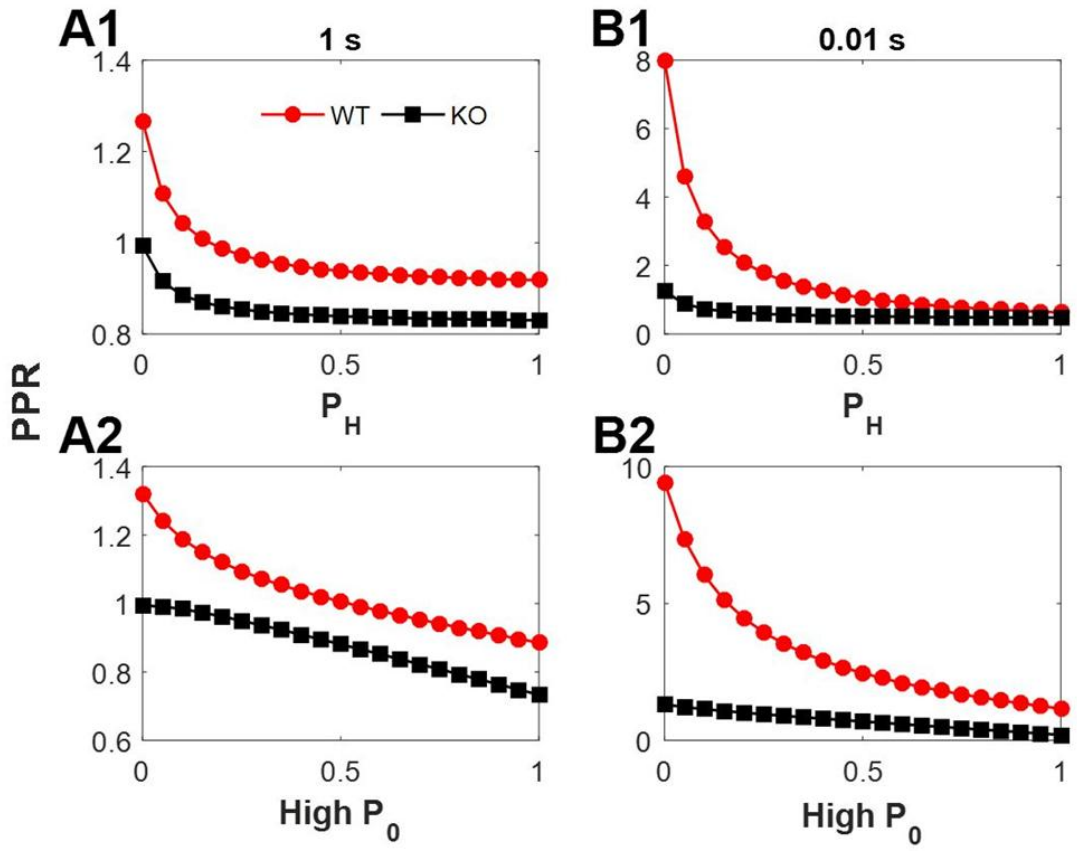
(A) PPR as a function of PH (0 - 1) and high P0 (four levels, 0.1, 0.25, 0.5 and 1). (B) PPR as a function of high P_0 (0 - 1) and PH (four levels, 0.1, 0.25, 0.5 and 1). Other parameters are held at their estimated levels. The black dashed line indicates the balance between facilitation and depression. AP: Action potential; P_H: fraction of release sites with high initial release probability; P_0: initial release probability.



Additional Figure 3 Pair-pulse ratios (PPRs) at 0.1 second inter-action potential interval as a function of P_H and high P_0. (A) PPR as a function of P_H (0 - 1) and high P_0 (four levels, 0.1, 0.25, 0.5 and 1). **(B)** PPR as a function of high P_0 (0 - 1) and P_H (four levels, 0.1, 0.25, 0.5 and 1). Other parameters are held at their estimated levels. The black dashed line indicates the balance between facilitation and depression. AP: Action potential; P_H: fraction of release sites with high initial release probability; P_0: initial release probability.



Additional Figure 4 Pair-pulse ratios (PPRs) at 1 second inter-action potential interval as a function of P_H and high P_0. (A) PPR as a function of P_H (0-1) and high P_0 (four levels, 0.1, 0.25, 0.5 and 1). **(B)** PPR as a function of high P_0 (0 - 1) and P_H (four levels, 0.1, 0.25, 0.5 and 1). Other parameters are held at their estimated levels. The black dashed line indicates the balance between facilitation and depression. AP: Action potential; P_H: fraction of release sites with high initial release probability; P_0: initial release probability.



Additional Figure 5 Pair-pulse ratios (PPRs) between wild-type (WT) and Syt7 knockout (KO) condition.

The difference in PPR initially decreases and then becomes constant for **(A1)** PPR at 1 second inter-action potential interval as a function of P_H (0 - 1) and (**A2)** PPR at 1 second inter-action potential interval as a function of high P_0 (0 - 1). The difference in PPR always decreases for **(B1)** PPR at 0.01 second inter-action potential interval as a function of P_H (0 - 1) and (**B2)** PPR at 0.01 second inter-action potential interval as a function of high P_0 (0 - 1). P_H: Fraction of release sites with high initial release probability; P_0: initial release probability.